Forced midexpiratory flow between 25% and 75% of forced vital capacity is associated with long-term persistence of asthma and poor asthma outcomes

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Background: Whether small-airway obstruction contributes to the long-term evolution of asthma remains unknown.

Objectives: Our aim was to assess whether the level of forced midexpiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) was associated with the persistence of current asthma over 20 years and the subsequent risk for uncontrolled asthma independently of FEV_1.

Methods: We studied 337 participants (142 children and 225 adults) with current asthma (asthma attacks or treatment in the past 12 months) recruited to the Epidemiological Study on the Genetics and Environment of Asthma (EGEA1) and followed up at the 12- and 20-year surveys. Persistent current asthma was defined by current asthma reported at each survey. A lung function test and a methacholine challenge test were performed at EGEA1 and EGEA2. Adjusted odds ratios (ORs) were estimated for FEF_{25-75} decreased by 10% of predicted value.

Results: A reduced level of FEF_{25-75} at EGEA1 increased the risk of long-term asthma persistence (adjusted OR, 1.14; 95% CI, 1.00-1.29). In children the association remained significant after further adjustment for FEV_1 and in participants with FEV_1 of greater than 80% of predicted value. A reduced FEF_{25-75} level at EGEA1 was significantly associated with more severe bronchial hyperresponsiveness ($P < .0001$) and with current asthma a decade later, with an association that tended to be stronger in those with (adjusted OR, 1.44; 95% CI, 1.14-1.81) compared with those without (adjusted OR, 1.21; 95% CI, 1.05-1.41) asthma exacerbation.

Conclusion: Our analysis is the first to suggest that small-airway obstruction, as assessed based on FEF_{25-75}, might contribute to the long-term persistence of asthma and the subsequent risk for poor asthma outcomes independently from effects of the large airways. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, small airways, FEF_{25-75}, epidemiology, longitudinal*

Asthma is a chronic inflammatory lung disease characterized by airway obstruction. It has long been considered that the middle and large airways are predominantly involved in asthma. In the last years, there has been renewed interest in the role of small-airways abnormalities in patients with chronic obstructive diseases, including asthma.[1,2]

The small airways are defined as those less than 2 mm in caliber. These airways, which are difficult to assess and treat in asthmatic patients and have a minimal contribution to overall lung resistance, were labeled the "quiet zone."[3] Different noninvasive methods to assess the small airways have recently been reviewed.[4,5] By using spirometry, forced midexpiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) is considered more reflective of the small airways than FEV_1.[6] Compared with FEV_1, which is a reproducible and appropriate measure of airway obstruction, FEF_{25-75} has been much less studied in epidemiologic and clinical studies. Nonetheless, previous studies suggested a clinical significance of this measure in managing childhood asthma[7] and in deciphering the cause of poor lung function both in children and adults.[8,9]

The literature supports a role for small-airways dysfunction on the clinical expression of asthma, including worse asthma control[10-13] and a higher number of exacerbations.[7,14] All these

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Data collection and analysis funded in part by the Hospital Program of Clinical Research (PHRC)–Paris, PHRC-Grenoble, National PHRC 2012, the scientific committee "AGIR pour les Maladies Chroniques," Merck Sharp & Dohme (MSD), and the GA^{2}LEN project (Global Allergy and Asthma European Network).

Disclosure of potential conflict of interest: V. Siroux receives research support from the Hospital Program for Clinical Research and AGIR "pour les Maladies Chroniques" and receives speakers' fees from Edimark Sante and Teva. S. Chanoine receives travel support from Actelion France, GlaxoSmithKline, Chiesi, and LFB. J. Bousquet serves as a consultant for Actelion, Almirall, Meda, Merck, Merck Sharp Dohme, Novartis, Sanofi-Aventis, Takeda, Teva, and Uriach. J. Just serves as a board member for Novartis and ALK-Abelló and receives speakers' fees from Novartis, ALK-Abelló, Stallergenes, and Chiesi. R. Nadif provides expert testimony for Anses and receives research support from the Hospital Program for Clinical Research. C. Pison receives consulting fees and travel support from AstraZeneca France, GlaxoSmithKline France, Novartis France, and Boehringer Ingelheim France. I. Pin receives speakers' fees from GlaxoSmithKline and Novartis and travel support from GlaxoSmithKline, Novartis, and Chiesi. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 6, 2015; revised September 21, 2015; accepted for publication October 27, 2015.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.10.029

Abbreviations used
BHR: Bronchial hyperresponsiveness
EGEA: Epidemiological Study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy
FEF_{25-75}: Forced midexpiratory flow between 25% and 75% of forced vital capacity
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
OR: Odds ratio

studies considered cross-sectional associations or a short-term follow-up of a few months. As recently underlined, the contribution of small-airways abnormalities in the clinical expression of asthma remained to be assessed, both in a cross-sectional and longitudinal manner.[15] In particular, how small-airways function drives the long-term evolution of asthma or the long-term subsequent risk of asthma control has not been addressed yet.[16]

Our aim was to assess the association of FEF_{25-75} levels with the persistence of current asthma in children and adults followed for 20 years, the subsequent risk for uncontrolled asthma, and the severity of bronchial hyperresponsiveness (BHR) while taking FEV_1 into account. We hypothesized that small-airway obstruction contributes, independently of FEV_1, to the long-term evolution of asthma and poor asthma outcomes.

METHODS

Population

The Epidemiological Study on the Genetics and Environment of Asthma (EGEA; https://egeanet.vjf.inserm.fr) is a French cohort including a group of asthmatic patients with their first-degree relatives and a group of control subjects recruited in the early 1990s and followed up for 20 years.[17] In total, 2047 adults and children were recruited from 1991 to 1995 (EGEA1). A first follow-up of the EGEA population was conducted from 2003 to 2007 (EGEA2; 1845 subjects),[18] and a second follow-up was conducted from 2011 to 2013 (EGEA3; 1558 subjects). All surveys included a detailed respiratory questionnaire (self-completed in EGEA3), and the 2 first surveys included lung function testing, measure of bronchial responsiveness, skin prick tests, and total IgE measurement. No follow-up bias related to asthma status and asthma-related phenotypes was observed.[19] A rich biobank, including blood samples, has been constituted (BB-0033-00043). The EGEA study was approved by the appropriate ethics committees.

The current analysis was conducted among 367 patients with current asthma at EGEA1 and with available current asthma status at the 12- and 20-year follow-up studies (142 children and 225 adults, Fig 1).

Phenotypes

Lung function tests were performed by trained research technicians using a standardized protocol and the European Community Respiratory Health Survey standard operating procedures. Briefly, forced spirometry was performed with regularly calibrated spirometers (Biomedin Srl, Padua, Italy; *Spirometer Masterscreen*, Jaeger at EGEA1 and *SpiroDyn'R*, Dyn'R at EGEA2). All measurements were corrected for body temperature, pressure, and saturation. Measurements were performed with the subject sitting straight and wearing a nose clip. The best of 5 forced expirations (FEV_1 plus forced vital capacity [FVC]) was selected, according to the American Thoracic Society/European Respiratory Society guidelines.[20] Prebronchodilator spirometric data were considered in this analysis. Study of the reproducibility of the spirometric variables showed a coefficient of variation for the best 2 loops (defined by the maximum value for FEV_1 plus FVC) of 2.1%, 2.4%, and 5.8% for FEV_1, FVC, and FEF_{25-75}, respectively, at EGEA1 (n = 811) and 1.5%, 2.0%, and 6.2%, respectively, at EGEA2 (n = 1190). Percent predicted values were computed by using Global Lung Initiative equations.[21]

For subjects with FEV_1 of 80% of predicted value or greater, a methacholine bronchial challenge test was performed (maximum cumulative dose, 4 mg). The severity of BHR was assessed by using the log slope calculated by regressing the percentage decrease in FEV_1 on a $\log_{10}$ dose and further transformed to satisfy the assumption of standard statistical analysis (normality and homogeneity of variance) by using the following transformation:

$$(100/(\text{Log slope}+10)).$$[22]

A lower slope indicates greater BHR severity.

Subjects with a positive answer to the questions "Have you ever had attacks of breathlessness at rest with wheezing?" or "Have you ever had asthma?" or subjects recruited as asthma cases were defined as having *ever asthma* at EGEA1. *Current asthma* was defined by the report of having had asthma attacks or asthma treatment in the past 12 months. *Persistent current asthma* was defined as current asthma reported at each time point (EGEA2 and EGEA 3). The others groups (not reported current asthma at EGEA2, EGEA3, or both) were defined as being in remission, including both transient and persistent remission.

Asthma symptom control has been assessed in 3 classes by using responses to EGEA2 survey questions to approximate the Global Initiative for Asthma 2015 definition as closely as possible. Subjects were defined as having controlled, partly controlled, and uncontrolled asthma if they had none, 1 to 2, or 3 to 4 of the following criteria, respectively: frequent daytime symptoms (defined by ≥1 asthma attack or ≥1 episodes of trouble breathing per week in the past 3 months), any nighttime symptoms (defined as waking because of asthma or an attack of shortness of breath in the last 3 months), frequent use of reliever medication (defined, on average, as more than twice a week in the past 3 months), and any activity limitation (defined by the following answers: "totally limited," "extremely limited," "very limited," "moderate limitation," and "some limitation" to the question "Overall, among all the activities that you have done during the last two weeks, how limited have you been by your asthma?").

Asthma exacerbation was defined at EGEA2 by means of either hospitalization for asthma or the use of oral steroids for breathing difficulties in the past 12 months.

Statistical/strategy of analysis

The longitudinal association between FEF_{25-75} percent predicted at EGEA1 and the long-term persistent current asthma phenotype, taking into account the 20-year follow-up data, was assessed by using logistic regression model. The association between FEF_{25-75} percent predicted and asthma control phenotypes was assessed in a cross-sectional way at EGEA2. We further estimated the longitudinal association between the level of FEF_{25-75} percent predicted at EGEA1 and the subsequent risk for partly/uncontrolled asthma and asthma exacerbation assessed at EGEA2 about 12 years later.

FEF_{25-75} percent predicted was first studied as a continuous variable (odds ratios [ORs] were expressed as the risk associated with each decrease of 10% in the level of FEF_{25-75} percent predicted), and although less statistically powerful, a secondary analysis was conducted by using the 70% threshold. Both cross-sectional and longitudinal analyses were first conducted in the whole studied population and then among participants with preserved FEV_1 defined by an FEV_1 of 80% of predicted value or greater. To provide a direct comparison between FEF_{25-75} and more widely used spirometric measures (FEV_1 and FEV_1/FVC ratio) in terms of their magnitude of association with asthma control outcomes, we estimated the ORs for an increment of 1 SD of each parameter.

Any multiple regression model considered age (continuous), sex, body mass index (continuous), allergic sensitization (≥1 positive skin prick test response to any of the 11 allergens at EGEA1 [cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*, olive, birch, *Parietaria judaica*, timothy grass, ragweed pollen, *Aspergillus* species, *Cladosporium herbarum*, and *Alternaria tenuis*] and 12 allergens [cypress added] at EGEA2), smoking status (never, exsmoker, and current smoker), allergic rhinitis (ever when assessed at EGEA1 and active when assessed at EGEA2), and age at asthma onset (≤4,